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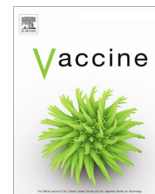
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Potential impact of maternal vaccination on life-threatening respiratory syncytial virus infection during infancy[☆]

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ABSTRACT

Background: Respiratory syncytial virus (RSV) infection is an important cause of infant mortality. Here, we estimated the potential impact of maternal vaccination against RSV on life-threatening RSV infection in infants.

Methods: We developed a mathematical model for maternal vaccine-induced antibody dynamics and used characteristics of a maternal RSV vaccine currently in phase 3 of clinical development. The model was applied to data from two cohorts of children younger than 12 months with RSV-related paediatric intensive care unit (PICU) admission in the United Kingdom (n = 370) and the Netherlands (n = 167), and a cohort of 211 children younger than 12 months with RSV-related in-hospital death from 20 countries worldwide.

Results: Our model predicted that, depending on vaccine efficiency, maternal vaccination at 30 weeks' gestational age could have prevented 62–75% of RSV-related PICU admissions in the United Kingdom and 76–87% in the Netherlands. For the global mortality cohort, the model predicted that maternal vaccination could have prevented 29–48% of RSV-related in-hospital deaths. Preterm children and children with comorbidities were predicted to benefit less than (healthy) term children.

Conclusions: Maternal vaccination against RSV may substantially decrease life-threatening RSV infections in infants.

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1. Introduction

Respiratory syncytial virus infection (RSV) is an important cause of morbidity and mortality in young children [1,2]. Globally, it is estimated that 48,000–74,500 children aged younger than five years died in-hospital with RSV-related lower respiratory tract infection in 2015 [2]. About 99% of RSV-related childhood mortality occurs in developing countries [2]. Most RSV-related mortality

occurs during the first year of life [3–6]. In our recent global case series study of 358 children with RSV-related in-hospital death, median age at death varied from 4 to 7 months depending on income region (upper middle-income vs. high-income countries, respectively) [6]. Preterm children and children with comorbidities such as congenital heart disease or chronic lung disease are at increased risk for severe RSV infection or even fatal RSV infection [7–10].

Maternal vaccination is currently being considered for RSV prevention in young children [11]. Maternal vaccination will only provide temporary protection due to an age-dependent decrease of maternally-acquired protective antibodies after birth [12,13]. For example, serological studies from Bangladesh and Kenya reported maternally-acquired protective antibodies against RSV to be present only up to four months after birth [14–16]. Similarly, maternal

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vaccination against influenza and pertussis provides protection during the first two to three months of life [12,17]. As transplacental antibody transfer becomes efficient only from the third trimester of pregnancy onward, maternal vaccination may provide limited protection for preterm infants [18–20]. To date, the potential impact of a maternal RSV vaccine on RSV-related mortality in young children is unknown. In this observational, retrospective study, we developed a mathematical model for maternal vaccine-induced antibody dynamics, taking into account transplacental antibody transfer rates and antibody decline after birth [15,18,21–24]. We applied this model to data from two retrospective cohorts of children with RSV-related paediatric intensive care unit (PICU) admission and a previously published cohort of children with RSV-related in-hospital death [6] and predicted the percentage of life-threatening RSV infections potentially prevented by maternal vaccination.

2. Methods

To predict the percentage of life-threatening RSV infections potentially prevented by maternal vaccination we developed a mathematical model for maternal vaccine-induced antibody dynamics, taking into account transplacental transfer rates of protective antibodies during pregnancy and antibody decline in newborn children.

2.1. Maternal vaccine-induced antibodies

Vaccination of pregnant women against RSV infection induces an increase in maternal anti-RSV antibodies. For simplicity, maternal vaccine-induced RSV-specific antibody levels were modelled as an exponential increase between day 7 and day 21 post-vaccination, and were assumed to stay constant afterward [15,21,22]. We hence modelled maternal vaccine-induced RSV-specific antibody levels (a_m in $\mu\text{g/ml}$) as follows (Fig. 1A):

$$\text{if } t < 7, \quad a_m(t) = a_{m0}$$

$$\text{if } 7 \leq t \leq 21, \quad a_m(t) = a_{m0} e^{(t-7) \log(f)/14}$$

$$\text{if } t > 21, \quad a_m(t) = a_{m0} f$$

where t is the time in days since vaccination, a_{m0} the natural level of maternal RSV-specific antibodies in $\mu\text{g/ml}$, and f the vaccine-induced fold increase in maternal RSV-specific antibodies (later referred to as vaccine efficiency).

2.2. Transfer of maternal antibodies

During pregnancy, maternal immunoglobulin G (IgG) antibodies are transferred to the foetus by transplacental transport. Transplacental transfer is thought to increase during pregnancy to become most efficient during the third trimester, and at term foetal IgG concentrations typically even exceed maternal IgG levels [18–20,25]. Based on published data on maternal and foetal IgG antibody levels at different time points during pregnancy (Section 5 and Fig. 3 (IgG1) of Palmeira et al. [26] which are based on Fig. 2 of Malek et al. [18]), we chose to model maternal IgG antibody transfer with an exponential function, as it gave the best description of the experimental data [18]. The parameters of this function were estimated using the function *lm* in R software (version 3.3.2) after a log-transformation of the data and the best fit of this model to the experimental data was found for:

$$r(t) = e^{-4.97+0.13t}$$

where r is the foetus-to-mother IgG transfer ratio and t is time in days since the beginning of pregnancy (Fig. 1B).

2.3. Foetal antibody levels after birth

We assumed that maternally-derived RSV-specific antibody levels in umbilical cord blood at birth (a_{cb} in $\mu\text{g/ml}$) can be calculated directly from the RSV-specific antibody levels in the mother and the foetus-to-mother IgG transfer ratio at time t_b , the gestational age (i.e. time of birth) in days, using the following function:

$$a_{cb}(t_b) = a_m(t_b) \cdot r(t_b)$$

After birth, maternally-acquired RSV-specific antibody levels in the new-born were assumed to decrease with a half-life $t_{1/2}$. The RSV-specific antibody levels of new-born children (a_c in $\mu\text{g/ml}$) can therefore be described as follows (Fig. 1C):

$$a_c(t) = a_{cb}(t_b) \left(\frac{1}{2}\right)^{t/t_{1/2}}$$

where t is the age of the new-born child in days after birth.

2.4. Model parameterization

Similar antibody dynamics for maternal vaccine-induced RSV-specific IgG and palivizumab competing antibody (PCA) have been reported [21,27] and as more data are available for PCA we decided to parameterize our model on PCA. A natural PCA level a_{m0} of 33 $\mu\text{g/ml}$ was used based on the phase-2 trial studying the safety and immunogenicity of a recombinant RSV fusion protein nanoparticle vaccine (RSV F vaccine) candidate in non-pregnant women of childbearing age [21]. PCA levels after vaccination against RSV have been reported to be 6.9–7.9-fold higher than the natural PCA level, depending on vaccine dosing [21]. Based on these values, we considered two vaccine efficiencies (f) of 5 and 10 in our simulations. RSV-specific antibody half-life after birth was reported to be 41 days by maternal RSV F vaccine manufacturers [23], which is in close agreement with reported values of 36–38 days in clinical studies measuring cord blood and infant maternally-acquired RSV-specific antibody levels [15,28]. A child PCA level of 40 $\mu\text{g/ml}$ was considered as the protective threshold against life-threatening RSV infection [24,29,30].

2.5. Study population

We applied our model to three independent, retrospective cohorts of patients. Anonymised secondary patient data were obtained through retrospective review of medical records. The first and second cohort consisted of children aged younger than 12 months with community-acquired RSV infection admitted to the PICU for mechanical ventilation, who all survived. The first cohort consisted of 370 children admitted to a PICU in the United Kingdom (UK) between 2002 and 2014 and the second cohort consisted of 167 children admitted to two PICUs in the Netherlands between 2008 and 2015. None of the children had received palivizumab during infancy. In the third cohort, children were selected from a retrospective case series study describing global, in-hospital, RSV-related mortality in 358 children aged younger than five years [6]. All children aged younger than 12 months with available data for prematurity were included. This resulted in a study population of 211 children with RSV-related in-hospital death from 20 countries. In the second and third cohort, when the exact gestational age was missing (i.e. for 60 term children in the Dutch PICU cohort and for 19 preterm and 85 term children in the mortality cohort) it was imputed to 34 or 40 weeks of gestation for preterm or term children respectively, based on median values of children with complete gestational age data.

For each cohort, we defined the following subgroups: children with comorbidities, healthy term children (born without

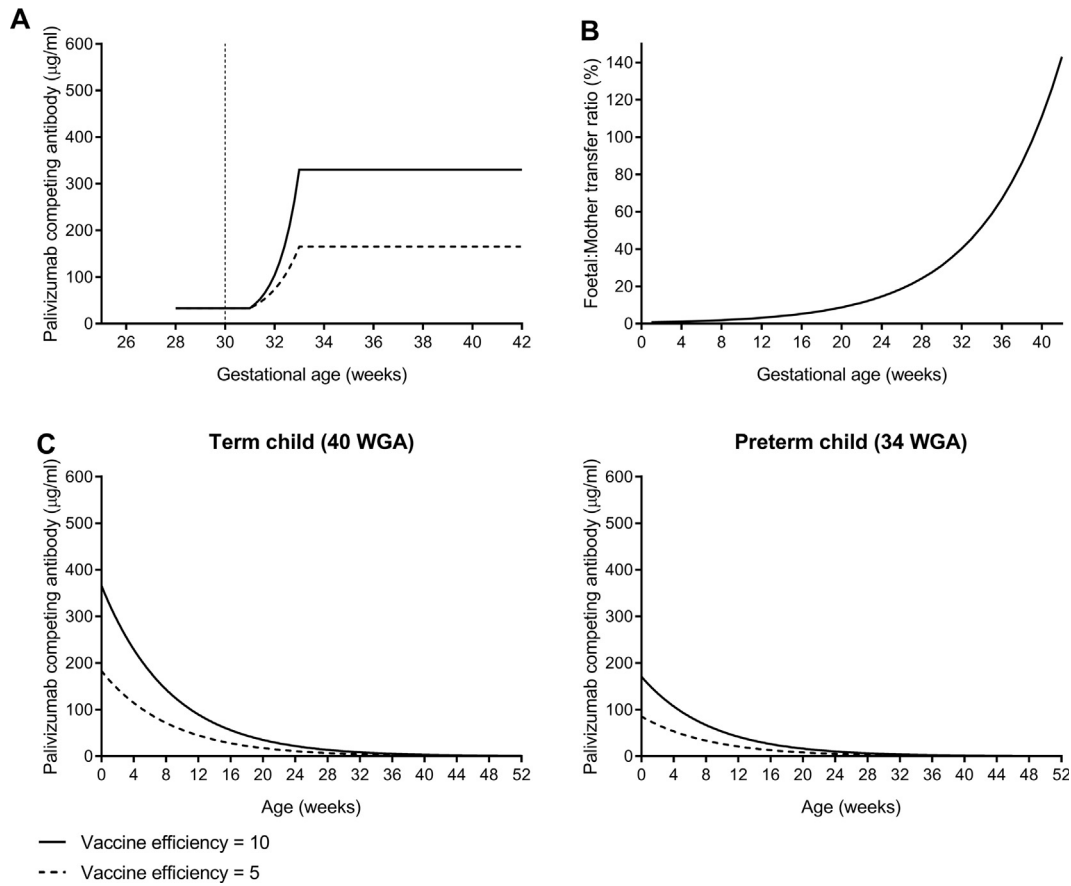


Fig. 1. Antibody levels after maternal vaccination in mother and child. (A) Vaccine-induced maternal antibody levels for maternal vaccination at 30 weeks' gestational age (WGA). (B) Transplacental antibody transfer during pregnancy. (C) Maternally-acquired antibody levels after birth for maternal vaccination at 30 WGA for a term child (born at 40 WGA) and a preterm child (born at 34 WGA).

comorbidities, at 37 weeks' gestational age or later) and healthy preterm children (born without comorbidities, earlier than 37 weeks' gestational age). For the global mortality cohort, countries were categorized as (i) high income, (ii) upper middle income, and (iii) lower middle or low income, on the basis of the World Bank classifications for 2016 [31].

2.6. Prediction of life-threatening RSV infections prevented by maternal vaccination

To predict the percentage of children with life-threatening RSV infection that could be prevented by maternal vaccination, we assumed that all mothers were vaccinated during pregnancy and used gestational age and age at RSV-related outcome (PICU admission or death). The general recommendation for maternal vaccination against pertussis is to vaccinate during the late-second or early-third trimester of pregnancy [32,33], while future maternal RSV vaccination is suggested during the third trimester [23]. Therefore, to evaluate the effect of timing of maternal vaccination, we first considered a large window for maternal vaccination between 22 and 40 weeks of gestation and then reported results on maternal vaccination at 30 weeks of gestation as a reflection of the recommendation to vaccinate during the early-third trimester of pregnancy.

For each child, we predicted the antibody level at birth taking into account timing of maternal vaccination, vaccine efficiency and gestational age at birth and then modelled antibody level decline until the observed time of RSV-related outcome (age at

PICU admission or death). We considered that a RSV-related outcome would be prevented (or at least postponed) if the simulated vaccine-derived protective antibody level was above the protective threshold at the time of outcome.

3. Results

3.1. Study population

Among the 370 children with RSV-related PICU admission for mechanical ventilation in the United Kingdom, 107 (29%) were born preterm and median age at the time of PICU admission was 49 days (InterQuartileRange (IQR) 30–88) (Table 1). In the Dutch cohort of children admitted to the PICU, 35 (21%) were born preterm and median age at the time of PICU admission was 38 days (IQR 27–63). The prevalence of comorbidity was reported to be 28% ($n = 102$) for the PICU cohort from the United Kingdom and 11% ($n = 19$) for the PICU cohort from the Netherlands.

Among the 211 children with global, RSV-related in-hospital death, 51 (24%) were born preterm and median age at the time of RSV-related death was 4 months (IQR 2–7). In the global mortality cohort, comorbidities were reported for 103 (49%) children, and 103 (49%) children were from high-income countries (Table 1). Median length of stay in hospital for children with RSV-related in-hospital death was 9 days (IQR 4–22, $n = 205$). For each cohort, the distributions for gestational age (GA) and age at RSV-related outcome (PICU admission or death) are shown in Fig. 2.

Table 1

Clinical characteristics in children with RSV-related PICU admission or in-hospital death.

	PICU cohort from the United Kingdom	PICU cohort from the Netherlands	Global mortality cohort
N	370	167	211
Male sex	222 (60)	94 (56)	116 (55)
Age at RSV-related outcome ^a (days)	49 [30–88]	38 [27–63]	122 [61–213]
Prematurity (<37 WGA)	107 (29)	35 (21)	51 (24)
Gestational age (weeks)	40 [36–40]	40 [37–40]	40 [37–40]
<i>Comorbidity status</i>			
Comorbidity	102 (28)	19 (11)	103 (49)
Healthy and term	182 (49)	117 (70)	78 (37)
Healthy and preterm	86 (23)	31 (19)	30 (14)
<i>Country of origin</i>			
Low-income or lower middle-income			60 (28)
Upper middle-income			48 (23)
High-income	370 (100)	167 (100)	103 (49)

Data are n (%) or median [IQR]. RSV = respiratory syncytial virus. PICU = paediatric intensive care unit.

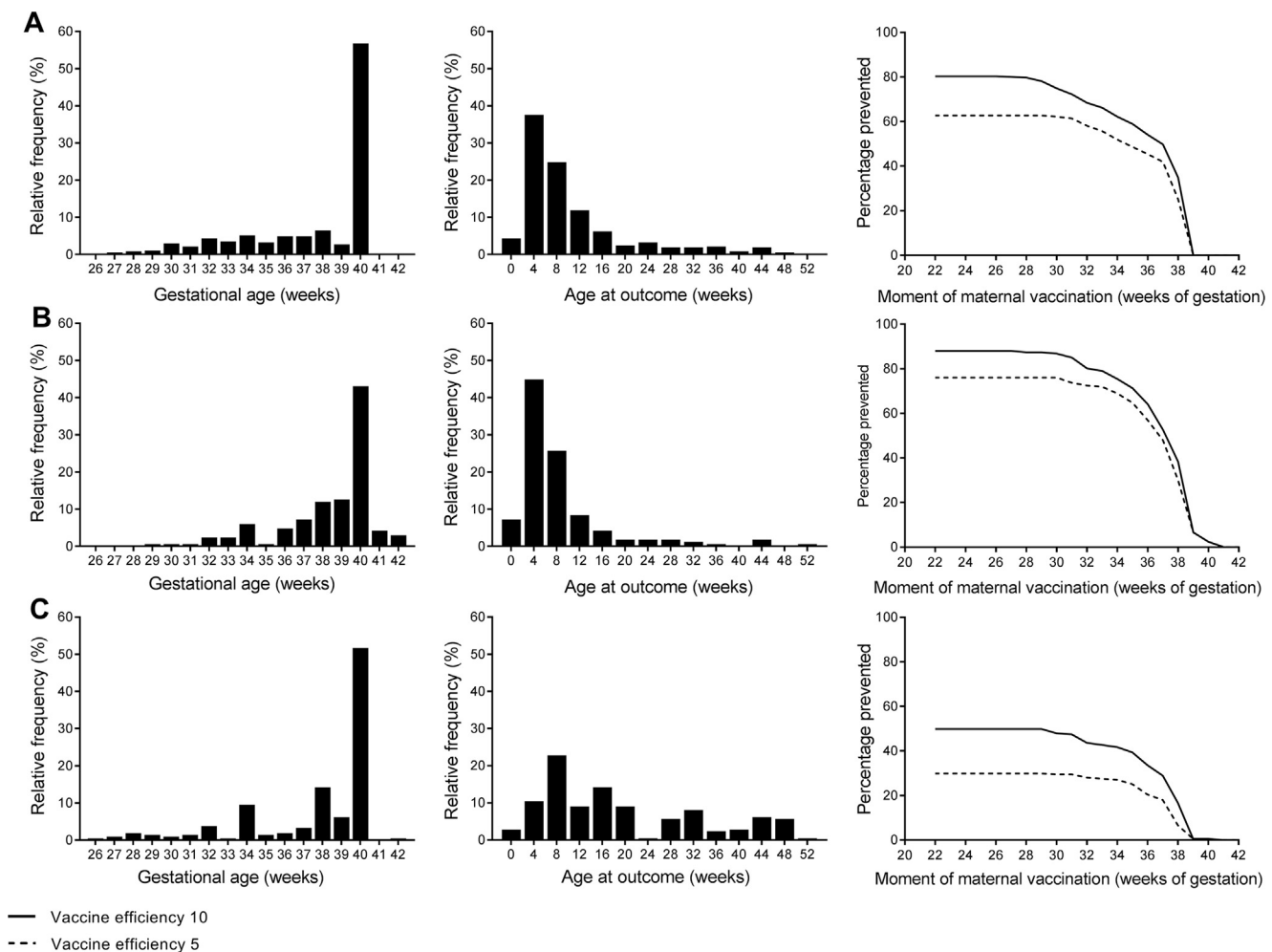
^a PICU admission or death.

Fig. 2. Distribution of gestational age and age at outcome and the predicted percentage of children with life-threatening RSV infection prevented by maternal vaccination for each cohort. Gestational age in weeks (left), age at outcome in weeks (middle) and predicted percentage of prevented cases are plotted for (A) PICU cohort from the United Kingdom ($n = 370$), (B) PICU cohort from the Netherlands ($n = 167$) and (C) Global mortality cohort ($n = 211$). The predicted percentages of prevented cases were calculated for two vaccine efficiencies ($f = 10$ solid line and $f = 5$ dashed line).

3.2. Percentage of life-threatening RSV infections prevented by maternal vaccination

We applied the mathematical model for maternal vaccine-induced antibody levels (see Section 2) to individual patient data

(gestational age and age at RSV-related outcome) from the three study cohorts. We hence predicted the percentage of outcomes that could have been prevented (or at least postponed) if mothers had been vaccinated between 22 and 40 weeks of gestation for two vaccine efficiencies ($f = 5$ and 10, see Section 2).

The model predicted that the percentage of cases prevented would be highest if the maternal vaccine would be administered between 22 and approximately 30 weeks' GA and would start to decrease for maternal vaccination after 30 weeks' GA as a result of the time required to reach maternal antibody peak levels (Fig. 2). The highest predicted percentage prevented was lower than 100% (80% in the UK cohort and 88% in the Dutch cohort with a vaccine efficiency of 10) and observed for maternal vaccination during the second trimester (between 22 and 26 weeks' GA). This resulted from the prevalence of prematurity and from age at PICU admission at which antibodies had already declined below the protective threshold. In the global mortality cohort, maternal vaccination during the second trimester would have prevented even fewer cases (maximum of 50% for a vaccine efficiency of 10). This lower percentage resulted from the higher age of children at RSV-related death (compared to the average age at PICU admission in the other two cohorts), leading to a larger proportion of RSV-related deaths occurring after antibody levels had already declined below the protective threshold. Therefore, vaccine efficiency had a larger impact on the percentage of cases prevented for the global mortality cohort than for the PICU cohorts.

According to our model, maternal vaccination at 30 weeks' GA would prevent at least 62% of RSV-related PICU admissions (62–75% in the United Kingdom and 76–87% in the Netherlands) and 29–48% of RSV-related in-hospital deaths, depending on vaccine efficiency (Fig. 2).

3.3. Impact of maternal vaccination on high-risk populations

We performed subgroup analyses to study the potential impact of maternal vaccination on high-risk populations such as preterm children, children with comorbidities and children from lower income regions. In preterm children, median age at the time of PICU admission was 53 days (IQR 32–78 and 37–80 for the United Kingdom and Netherlands respectively) and median age at the time of RSV-related in-hospital death was 122 days (IQR 61–183) (Supplemental Table 1). The model predicted that maternal vaccination, even if administered during the second trimester (i.e. 22–26 weeks' GA), would prevent a smaller percentage of preterm than term children in each cohort (Fig. 3). This is a direct consequence of the reduced transplacental antibody transfer relative to the time of birth for preterm children compared to term children. For preterm

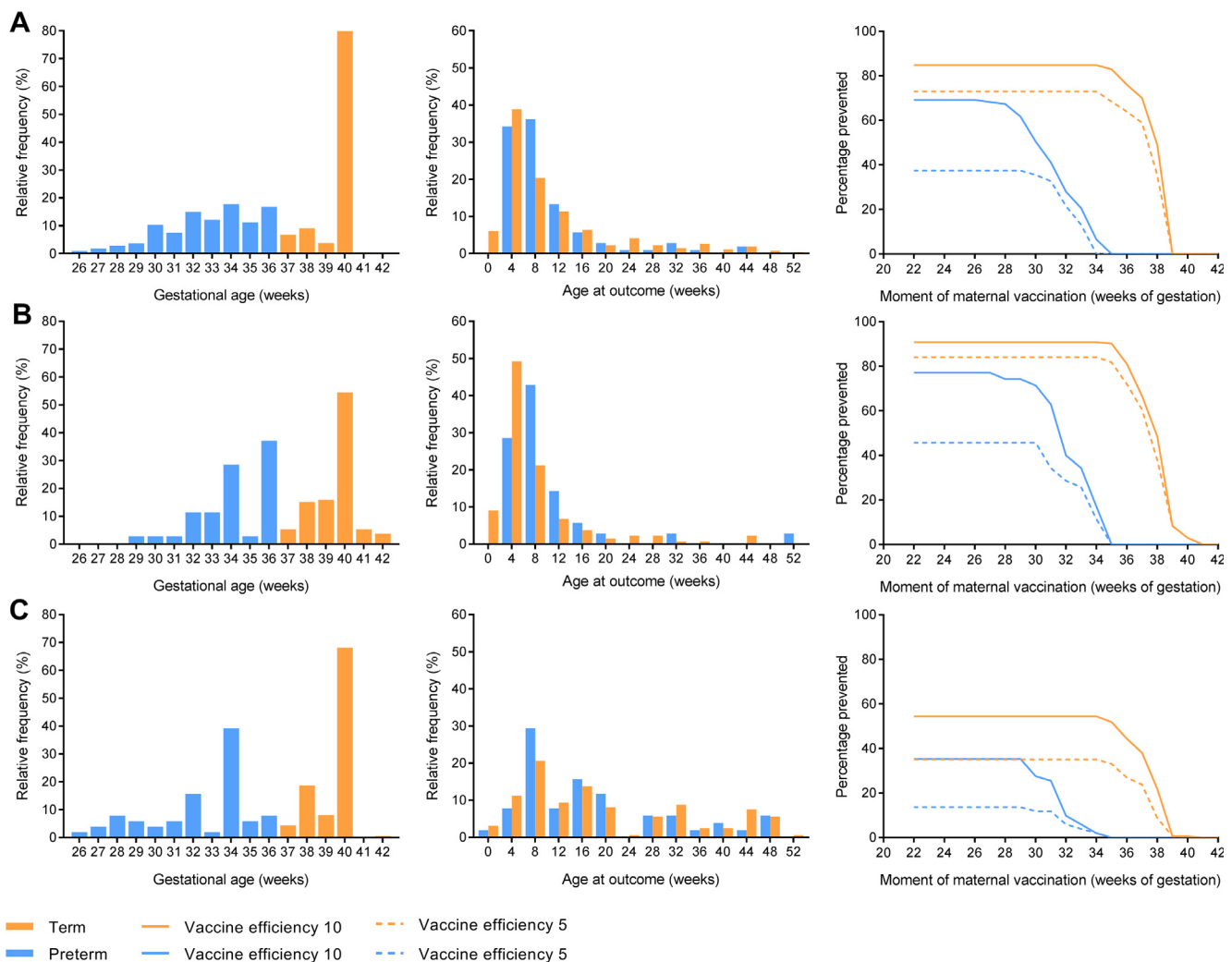


Fig. 3. Distribution of gestational age and age at outcome and the predicted percentage of children with life-threatening RSV infection prevented by maternal vaccination for each cohort stratified by prematurity status. Gestational age in weeks (left), age at outcome in weeks (middle) and predicted percentage of prevented cases are plotted for (A) PICU cohort from the United Kingdom (Term $n = 263$, Preterm $n = 107$), (B) PICU cohort from the Netherlands (Term $n = 132$, Preterm $n = 35$) and (C) Global mortality cohort (Term $n = 160$, Preterm $n = 51$). Term children are in orange and Preterm in blue. The predicted percentages of prevented cases were calculated for two vaccine efficiencies ($f = 10$ solid line and $f = 5$ dashed line).

children, maternal vaccination at 30 weeks' GA could have prevented 36–51% of RSV-related PICU admissions in the United Kingdom (vs. 73–85% in term children), 46–71% in the Netherlands (vs. 84–91% in term children), and 12–28% of RSV-related in-hospital deaths (vs. 35–54% in term children). Later vaccination would further decrease the percentage of prevented cases among preterm children.

Children with comorbidities tended to be older at the time of RSV-related PICU admission than healthy term children, whereas age at the time of RSV-related in-hospital death was similar for children with comorbidities and healthy term children (Supplemental Table 1). We found that children with comorbidities would benefit less from maternal vaccination than healthy term children regardless of the timing of maternal vaccination (Fig. 4). For the PICU cohort from the United Kingdom, maternal vaccination at 30 weeks' GA would have prevented PICU admission in 46–61% of children with comorbidities (53–68% in the Dutch cohort) compared to 81–91% of healthy term children (87–92% in the Dutch cohort). For the global mortality cohort, maternal vaccination at 30 weeks' GA would have prevented RSV-related in-hospital death

in 26–43% of children with comorbidities compared to 40–59% of healthy term children.

In children with RSV-related death from lower income regions (28% of the global mortality cohort), the predicted percentage of prevented in-hospital deaths was 30–50% for maternal vaccination at 30 weeks' GA and similar to that in children from other income regions (data not shown).

4. Discussion

We have developed a mathematical model to predict the percentage of children with life-threatening RSV infection during the first year of life that may be prevented by maternal vaccination. The model was calibrated using vaccine characteristics of a maternal RSV vaccine currently in phase 3 of clinical development and was applied to individual patient data for RSV-related PICU admission and death. The model predicts that maternal vaccination against RSV could substantially decrease life-threatening RSV infections in infants. Preterm children and children with comorbidities, those at increased risk for severe RSV, were predicted to

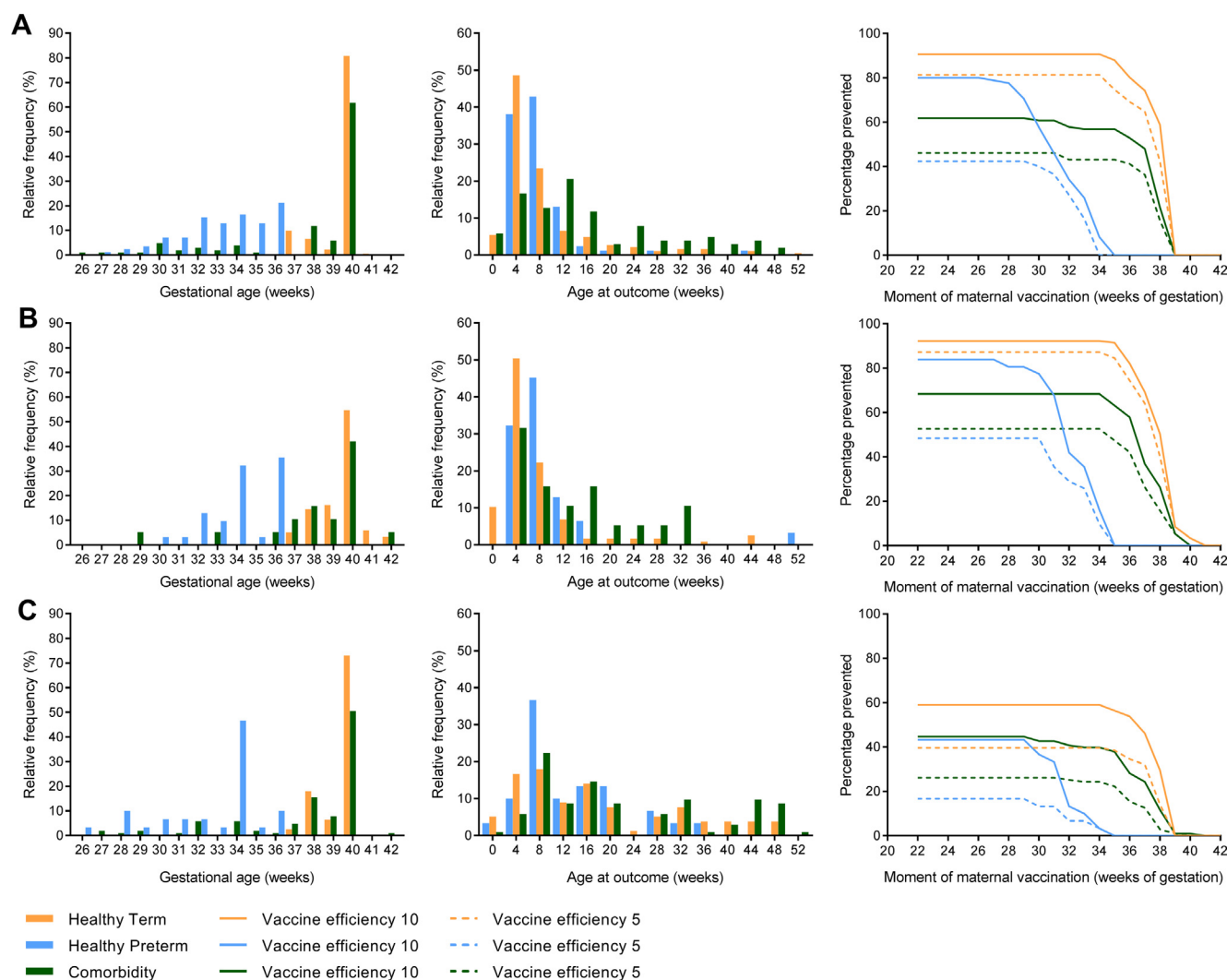


Fig. 4. Distribution of gestational age and age at outcome and the predicted percentage of children with life-threatening RSV infection prevented by maternal vaccination for each cohort stratified by comorbidity status. Gestational age in weeks (left), age at outcome in weeks (middle) and predicted percentage of prevented cases (right) are plotted for (A) PICU cohort from the United Kingdom (Healthy term $n = 182$; Healthy preterm $n = 86$; Comorbidity $n = 102$), (B) PICU cohort from the Netherlands (Healthy term $n = 117$; Healthy preterm $n = 31$; Comorbidity $n = 19$) and (C) Global mortality cohort (Healthy term $n = 78$; Healthy preterm $n = 30$; Comorbidity $n = 103$). Healthy term children are in orange, Healthy preterm in blue and Children with comorbidities in green. The predicted percentages of prevented cases were calculated for two vaccine efficiencies ($f = 10$ solid line and $f = 5$ dashed line).

benefit less from a maternal RSV vaccine than term and healthy children.

We assumed in the model that transplacental maternal antibody transfer increases during pregnancy and becomes most efficient during the third trimester and at term, as described by Malek et al. [18]. This assumption is in agreement with previous studies on transplacental transfer in preterm infants for other pathogens [19], and with a study examining the effectiveness of maternal pertussis vaccination in England, which observed limited benefit of maternal vaccination for preterm compared to term children [34]. In contrast, a recent study describing maternal RSV antibody levels in comparison to cord blood levels in 26 preterm infants found similar antibody levels in preterm and term children [25], suggesting that transplacental antibody transfer may already be efficient before the third trimester. Given the increased risk for severe RSV infection in preterm children and the relatively high prevalence of prematurity in lower income regions [35], where most RSV-related childhood mortality occurs [2], having a better knowledge of transplacental antibody transfer is essential to improve the prediction of the impact of maternal vaccination.

A strength of our study was the use of characteristics of a maternal RSV vaccine currently in development and of patient data from three independent cohorts. We were able to predict the percentage of prevented (or at least postponed) cases for the overall study population and for subgroups more at risk for life-threatening RSV infection, such as preterm children or children with comorbidities. This model was developed to study the impact of a specific maternal RSV vaccine, but may be used for other maternal vaccines by calibrating for specific vaccine characteristics.

Although we have based our model on current biological knowledge, some of the assumptions need further discussion. We did not incorporate RSV protective antibodies acquired by natural RSV infection during pregnancy or vaccine-induced protective antibodies in breastmilk. These factors may influence the antibody level in children and, therefore, protection against RSV. In addition, we did not incorporate vaccine coverage, RSV transmission patterns, risk of RSV-related disease or disease severity. A more classical approach such as the compartment model recently published by Hogan et al. [36] in combination with our approach would provide more insights into vaccine effectiveness at a population level. We applied the model to three cohorts of children with life-threatening RSV infection which has introduced selection bias. For example, high-risk groups, such as preterm children, likely have been overrepresented given their increased risk for severe RSV infection, whereas the exclusion of children who had received palivizumab prophylaxis may have resulted in underrepresentation of children with severe prematurity. Imputation of missing gestational age data and the inclusion of preterm children (20%) in the subgroup of children with comorbidities may also have influenced our results. The percentage of cases prevented, as predicted by our model, should therefore not be directly extrapolated to the general population. In addition, results may not be generalizable to lower income regions as the majority of children in our study were from high-income countries.

Several model assumptions may have resulted in an overestimation of the impact of maternal vaccination on life-threatening RSV infection. First, we assumed that antibody levels in the mother would exponentially increase from 7 days post-vaccination and reach a maximal level at 21 days post-vaccination. This level was assumed to stay constant through the rest of pregnancy [15]. If, however, antibody levels in the mother actually declined over time, antibody transfer to the foetus would be reduced and our model would overestimate the percentage of cases prevented by maternal vaccination. Additionally, if maternal antibody levels were to decline over time, this could

affect the optimal timing of maternal vaccination. Second, our model did not consider reduced transplacental transfer caused by maternal comorbidities, such as malaria or hypergammaglobulinemia [12]. Third, in our model for maternal vaccine-induced antibody dynamics, we assumed that the antibody half-life was 41 days, based on available maternal RSV vaccine phase-2 trial data [21], which is higher than reported by others [37]. When we considered an antibody half-life as short as 20 days, the percentage of prevented cases would be reduced (e.g. 11–24% instead of 35–56% of RSV-related in-hospital deaths for maternal vaccination at 30 weeks' GA). Fourth, we assumed full protection from life-threatening RSV infection as long as a child's predicted antibody levels remained above the protective threshold of 40 µg/ml [24,29,30]. However, the correlation between antibody levels and protection from RSV disease has not been well defined [15,38,39]. Fifth, our results describe the situation in which *all* mothers would have been vaccinated during pregnancy. When we considered a vaccine coverage of 60%, based on the observed vaccine coverage for maternal pertussis vaccination in the United Kingdom and Belgium [40,41], the percentage of prevented cases would be substantially lower (e.g. 42–48% and 50–54% instead of 62–75% and 76–87% of RSV-related PICU admissions in the United Kingdom and the Netherlands respectively for maternal vaccination at 30 weeks' GA). Finally, protection from RSV infection was assumed to result in prevention of RSV-related PICU admission or death, whereas for some children it may merely have postponed these RSV-related outcomes.

In summary, our mathematical model suggests that maternal vaccination against RSV could substantially decrease the number of life-threatening RSV infections in infants. In order to inform policy makers about the need for additional preventive interventions after birth for high-risk groups, such as preterm children, future studies on maternal vaccination should provide accurate data for transplacental antibody transfer per week of gestation, antibody half-life in new-born children and the protective antibody threshold.

Conflict of interest

All authors declare no conflict of interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2018.06.021>.

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